REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-13 have been cancelled, and claims 14-26 have been amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

Claims 14-26 are now pending in this application.

I. FORMAL MATTERS

The examiner objects to references A3 and A6 of the Information Disclosure Statement for allegedly lacking proper identification. For clarification, the abstract number of reference A3 is 154705n. Regarding reference A6, the reference notes that edema is a symptom that accompanies pancreatitis. Applicants are in the process of obtaining an English translation of the relevant part of the document and will forward it to the examiner as soon as it is available.

II. REJECTIONS UNDER 35 U.S.C. § 112 ¶1

The examiner rejects claims 14-24 and 26 under 35 U.S.C. §112, ¶1, for allegedly failing to enable one of ordinary skill in the art to make and use the invention. Applicants respectfully traverse the rejection.

Under §112, an application must explain how to "make and use" the claimed invention. The courts have interpreted this statute to mean that the specification must teach the skilled artisan how to practice the invention without undue experimentation. *See In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, the test is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of

experimentation is typical in the area. *See In re Wands*, 858 F.2d at 736-37. *See also* MPEP §2164.01 (Feb. 2003) at page 2100-179.

In levying an enablement rejection, the examiner has the burden of establishing why the scope of the claims is not adequately enabled by the specification. *See* MPEP §2164.04 (Feb. 2003), pg. 2100-183. Applicants respectfully argue that the examiner has failed to meet this burden.

The examiner has proffered no evidence that one skilled in the art at the time of the invention would need to exert undue experimentation to make and use the invention. Instead, the examiner merely declares out of hand that "the person of ordinary skill in the art would not expect that suppression of the effects of a single cytokine would completely stop or prevent a condition that is due to the effects of multiple cytokines." Office Action dated October 6, 2003, pg. 3, 2nd ¶. This statement falls well-short of establishing that the scope of the claims is not adequately enabled.

The specification describes how to make and prepare a variety of IL-6 antagonists. *See* Application, pg. 30-36. The specification further provides working examples demonstrating the effectiveness of IL-6 antagonists in preventing and/or treating pancreatitis. *Id.* at 29-30. Thus, one of skill in the art could practice the invention without undue experimentation.

Nevertheless, to expedite prosecution, applicants have amended the claims to encompass methods of treating pancreatitis and reducing pancreatic edema. Applicants believe the amendments obviate the pending rejection.

Applicants, however, specifically reserve the right to pursue claims to methods of preventing pancreatitis and suppressing pancreatic edema in one or more subsequent applications.

III. REJECTIONS UNDER 35 U.S.C. § 102(b)

The examiner rejects claims 1-13 under 35 U.S.C. §102(b) for allegedly being anticipated by Kishimoto *et al.* The examiner further rejects claims 1-4 and 6-13 under 35 U.S.C. §102(b) for allegedly being anticipated by Sato *et al.* Applicants have cancelled claims 1-13. Therefore, the rejections are now moot.

The examiner rejects claims 1, 11-14, 24 and 25 under 35 U.S.C. §102(b) for allegedly being anticipated by Reed *et al.* Applicants respectfully traverse the rejection.

Critical to the examiner's rationale for citing Reed is her conclusion that PYY is an IL-6 antagonist. Reed makes no such characterization of PYY, however. Reed does not describe whether: (1) the PYY decreases an IL-6 level resulting in a decrease of mortality, or (2) the PYY suppresses pancreatitis resulting in a decrease of IL-6 level. If the latter is the case, then PYY is not an IL-6 antagonist.

Moreover, contrary to the examiner's assertion, those of skill in the art at the time the claimed invention was made understood PYY to act directly on the pancreas and not as an IL-6 antagonist. For example, Tito *et al.* (Am. J. Surg. 165(6): 690-696 (1993); a copy of which is enclosed) describe the relationship between PYY and pancreatitis. According to Tito, PYY is an inhibitor of pancreatic secretion and cholecystokinin and acts on the pathophysiology of pancreatitis. Although the specific mechanism of PYY's effect on pancreatitis is unclear, Tito notes that "[w]e previously documented significant decreases in plasma PYY in sodium taurocholate-induced AP in the anesthetized pig, with exogenous PYY suppressing plasma amylase activity." In addition, Tito shows that PYY alleviates the symptom of pancreatitis induced by cerulein, which is an analog of cholecystokinin, and concludes "that as an inhibitor of pancreatic exocrine secretion, PPY ameliorates cerulean-induced pancreatic injury in the conscious rat." This suggests that PYY acts directly on the pancreas.

In this regard, Reed states that "[p]eptide YY(PYY) has multiple inhibitory actions on the proximal digestive tract, including inhibition of exocrine pancreatic secretion. Many of its effects oppose those of cholecystokine, which in supra maximal doses induces pancreatitis." From this, an artisan would have concluded that PYY acts *directly* on the pancreas *per se* so as to inhibit pancreatitis. Therefore, a decrease of early levels of circulating IL-6 in a necrotizing acute pancreatitis model by administering PYY, as shown in the Reed reference, would have been considered a result of alleviation of pancreatitis by PYY.

Thus, Reed does not teach or suggest treating pancreatitis with an IL-6 antagonist. Since Reed fails to contain each and every element of the claims, the reference cannot anticipate the claimed invention. Applicants, therefore, request that rejection be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. § 103

A. Rejection of the Claims Over Reed et al. in View of Sato et al. and/or Kishimoto et al.

The examiner rejects claims 15-23 and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Reed *et al.* in view of Sato *et al.* and/or Kishimoto *et al.* Applicants respectfully traverse the rejection.

A proper rejection for obviousness under §103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, or device, or carry out the claimed process, and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438 (Fed. Cir. 1991). In the pending case, the examiner has failed to establish a *prima facie* case of obviousness.

In particular, the examiner has failed to provide any objective evidence of record that an artisan at the time of the invention would have been motivated to combine the cited references to obtain the claimed invention. In asserting the combination, the examiner relied on the erroneous assertion that Reed taught the treatment of pancreatitis using an IL-6 antagonist. As noted above, Reed made no such teaching. Accordingly, the rejection should be withdrawn.

B. Rejection of the Claims Over Sato et al. and/or Kishimoto et al. in View of Gross et al. and Farkas et al.

The examiner also rejects claims 15-26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Sato *et al.* and/or Kishimoto *et al.* in view of Gross *et al.* and Farkas *et al.* Applicants respectfully traverse the rejection.

According to the examiner, Sato and Kishimoto provide antibodies against IL-6 receptors and teach the use such antibodies in the treatment of IL-6 related conditions. The examiner characterizes Gross as disclosing that IL-6 level increases in acute pancreatitis and Farkas as teaching "experimental acute pancreatitis results in increased blood-brain barrier permeability ... and that such is associated with increased IL-6 levels." Office Action, pg. 6,

2nd ¶. Without citing any evidence of a motivation to combine the references, the examiner concludes that "[t]he person of ordinary skill in the art would have expected success [at treating acute pancreatitis with antibodies against IL-6 receptors] because the primary references teach the antibodies for the express purpose of inhibiting IL-6 associated responses." *Id.* Applicants respectfully disagree with the Examiner's analysis and conclusion. One of ordinary skill in the art would not have been motivated to combine the cited references to obtain the claimed invention with a reasonable expectation of success.

As shown in the enclosed article by Mukaida *et al.* (original Japanese article and English translation are enclosed herewith): (1) a cytokine, such as interleukin-6, exhibits various biological actions (Pleiotropy); (2) a plurality of cytokines exhibit the same action on the same cell (Redundancy); and (3) a plurality of cytokines are involved in the same cell line depending on the process of differentiation and growth. *See* English translation, pg. 5, ln. 5-17. In addition, Bellomo (*Anaesthesia and Intensive Care*, 20(3): 288-302 (1992); enclosed herewith), taught that once a complicated network is activated, many cytokines belonging to the same network are produced.

Accordingly, at the time of the invention, an artisan would have expected that if an antagonist successfully blocked one cytokine, such as IL-6, another cytokine would likely compensate for the lost signal. Thus, for a given disease, such as pancreatitis, an artisan would not have reasonably expected that blocking a single cytokine would result in the prevention or amelioration of the disease. Indeed, the examiner voiced this same conclusion, noting that "the person of ordinary skill in the art would not expect that suppression of the effects of a single cytokine would completely stop or prevent a condition that is due to the effects of multiple cytokines ..." Office Action, pg. 3, ln. 6-10.

In the present case, applicants surprisingly and unexpectedly discovered that administering an IL-6 antagonist can effectively prevent or ameliorate pancreatitis. The cited art fails to suggest such a treatment. Moreover, as discussed above, the discovery was counter to the reasonable expectations of practitioners. Accordingly, applicants respectfully request that the rejections be withdrawn.

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Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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FOLEY & LARDNER LLP
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5571
Facsimile: (202) 672-5399

For Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264